clinical adverse events, by body system and COSTART terminology. If a patient experienced more than 1 episode of an adverse event, the patient was counted only once for that event. If a patient had more than 1 adverse event in a body system category, the patient was counted only once in that body system total.

No. (%) of Patients with Clinical Adverse Events by Body System: ALA-018

Body System Category/ Adverse Event (COSTART)	LEVULAN® (N=88)	Vehicle (N=29)
With Any Adverse Events	31 (35%)	12 (41%)
Body as a Whole	17 (19%)	8 (28%)
Accidental Injury	2 (2%)	0 (0%)
Allergic Reaction	1 (1%)	1 (3%)
Back Pain	1 (1%)	2 (7%)
Chest Pain	0 (0%)	1 (3%)
Cyst	1 (1%)	0 (0%)
Flu Syndrome	0 (0%)	2 (7%)
Headache	6 (7%)	1 (3%)
Hernia	1 (1%)	0 (0%)
Infection	4 (5%)	3 (10%)
Neck Pain	1 (1%)	0 (0%)
Unevaluable Event*	1 (1%)	0 (0%)
Cardiovascular System	0 (0%)	1 (3%)
Syncope	0 (0%)	1 (3%)
Digestive System	4 (5%)	0 (0%)
Diarrhea	2 (2%)	0 (0%)
Gastrointestinal Disorder	1 (1%)	0 (0%)
Tooth Disorder	1 (1%)	0 (0%)
Hemic and Lymphatic System	1 (1%)	0 (0%)
Abnormal Platelets	1 (1%)	0 (0%)
Metabolic and Nutritional System	1 (1%)	0 (0%)
Gout	1 (1%)	0 (0%)
Musculoskeletal System	1 (1%)	0 (0%)
Arthrosis	1 (1%)	0 (0%)

No. (%) of Patients with Clinical Adverse Events by Body System: ALA-018 (Continued)

Body System Category/ Adverse Event (COSTART)	LEVULAN® (N=88)	Vehicle (N=29)
Nervous System	3 (3%)	0 (0%)
Amnesia	1 (1%)	0 (0%)
Anxiety	1 (1%)	0 (0%)
Tremor	1 (1%)	0 (0%)
Respiratory System	4 (5%)	0 (0%)
Bronchitis	1 (1%)	0 (0%)
Laryngitis	1 (1%)	0 (0%)
Rhinitis	2 (2%)	0 (0%)
Skin and Appendages	6 (7%)	3 (10%)
Herpes Simplex	1 (1%)	0 (0%)
Lichenoid Dermatitis	1 (1%)	0 (0%)
Rash	1 (1%)	1 (3%)
Seborrhea	0 (0%)	1 (3%)
Skin Carcinoma	2 (2%)	1 (3%)
Skin Hypertrophy	1 (1%)	0 (0%)
Special Senses	2 (2%)	0 (0%)
Cataract NOS	1 (1%)	0 (0%)
Conjunctivitis	1 (1%)	0 (0%)

* Unevaluable event: This patient had 3 procedures associated with surgery (Pt.18219, Table 16.2.13)

The five patients in the LEVULAN® arm who experienced serious adverse events (patients 18102, 18219, 18221, 18402, and 18501) experienced broken left leg (from accident), implant of a thalamic stimulator (to treat a tremor), a pre-existing hyperkeratotic (Grade 3)actinic keratosis (at an untreated site), pre-existing squamous cell carcinoma on the left ear, and ruptured abdominal hernia. Investigators considered these episodes unrelated to exposure to LEVULAN®.

Conjunctivitis developed in one patient (no. 18711) 44 days after LEVULAN® application. The investigator concluded that it was not related to LEVULAN® treatment. Reviewer's Comment:

Reviewer's Comment:
With most topical medications, there is only one relevant period during which adverse events need to be assessed: the period of drug administration. In contrast, with LEVULAN®, three distinct periods must be assessed for the incidence and severity of adverse events: (a) [pre-PDT] the period from LEVULAN® application until light administration; (b) [peri-PDT]the period during and shortly after light administration; and (c) [post-PDT]the period from shortly after administration of light therapy to end-of-follow-up. The reason why adverse events within each of these three time periods must be

assessed separately is that the type and quantity of the adverse events differ. A timepoint useful for separating short- from long-term adverse events would be 24 hours after treatment, because for most patients the peri-PDT adverse events have resolved or returned to baseline by this timepoint.
Another complication in assessment of adverse event incidence and severity is that untreated actinic keratoses manifest some of the signs (e.g. erythema, hyper- and hypopigmentation) that are considered adverse events.

Adverse Events: pre-PDT

The percentage of patients who develop signs and/or symptoms of a photodynamic response (e.g., burning/stinging and/or edema) during the time interval between application of LEVULAN® and administration of blue light may be an indirect measure of the prevalence of an (inappropriate) photodynamic response that results from inadvertent exposure to ambient light. Despite the presence of information in the protocol that warns patients to protect the lesions being treated from light exposure for a minimum of 14 to 18 hours after application (i.e., "to avoid direct exposure of target sites to sunlight or other high intensity light sources, including tanning light devices"), active-treated patients do manifest signs/symptoms of a photodynamic response **prior** to blue light administration: 47% of active treatment patients develop burning/stinging between Baseline A and B, while 14% of vehicle treatment patients develop burning/stinging; 17% of active treatment patients develop edema between Baseline A and B, while no vehicle treatment patients develop edema between Baseline A and B.

Reviewer's Comment: The incidence and/or increased prevalence of burning/stinging and edema that develops between Baseline A and B is attributable either to irritancy or to an inappropriate photodynamic response. Since no irritancy study has been performed with the to-be-marketed formulation, it is not possible to discern which of these two alternative explanations is correct.

Adverse Events: peri-PDT

The medical reviewer analyzed the incidence of signs and/or symptoms expected during a photodynamic response from the period including Baseline B until 24 hours after light treatment for patients undergoing active and control treatment, as is depicted below.

Incidence of erythema, edema, and burning/stinging during and/or 24 hours after photodynamic therapy*: ALA-018

	FACE				SCALP			
	ACTIVE		VEHICLE		ACTIVE		VEHICLE	
Fraction of patients with some or all target lesions involved:	SOME	ALL	SOME	ALL	SOME	ALL	SOME	ALL
Erythema♦	8/72 (11%)	64/72 (88%)	12/21 (57%)	7/21 (33%)	2/16 (19%)	14/16 (81%)	4/8 (50%)	4/8 (50%)
Edema♦	23/72 (32%)	12/72 (17%)	0/21	0/21	5/16 (31%)	3/16 (19%)	0/8	0/8
Burning/Stinging	3/72 (4%)	68/72 (94%)	7/21 (33%)	2/21 (10%)	0/16	16/16 (100%)	1/8 (13%)	2/8 (25%)

*defined as the prevalence of adverse events during the time points at baseline B, through light treatment, and at 24 hours after light treatment

♦Sponsor has not collected data that would permit the classification of these adverse events as mild, moderate, or severe.

From Data Listings 15, 16, and 18, Vol. 1.56

Sponsor's analysis of the data listings (not shown) largely corroborated the medical officer's analysis. The consequence of treatment with LEVULAN® and blue light was to increase the prevalence of patients who experienced erythema, edema, and stinging/burning associated with treated lesions in the period during and shortly after photodynamic therapy.

As depicted in the following table, approximately half of the patients in whom all the target lesions were erythematous during and/or shortly after photodynamic therapy did not have all their target lesions erythematous at one week after treatment. The adverse events of edema and burning/stinging resolved more quickly, usually within 24 hours after completion of light therapy.

Patients with adverse events involving 100% of target lesions during photodynamic therapy: prevalence of erythema, edema, and burning/stinging at 24 hours and one week after therapy: ALA-018

	FACE				SCALP			
	ACTIVE		VEHICLE		ACTIVE		VEHICLE	
Fraction of patients with all target lesions involved:	24 hours	One week	24 hours	One week	24 hours	One week	24 hours	One week
Erythema	--	30/64 (47%)		2/7 (29%)		7/14 (50%)		2/4 (50%)
Edema		0/12				0/3		
Burning/Stinging	17/68 (25%)	1/68 (1%)	1/2	0/2	2/16 (13%)	0/16	0/2	0/2
From Data Listings 15, 16, and 18, Vol. 1.56								

In response to medical reviewer's request, sponsor submitted clinical slides showing the time course of healing in some of the patients treated with LEVULAN® in this trial. As judged from these slides, in several of these patients the erythema and edema arising post-PDT appeared to extend beyond the borders of the actinic keratosis. Of note, the application instructions in the protocol state: "gently dab the lesions designated to be treated being certain to uniformly wet the entire lesion including the margin (Appendix E: Application Instructions). The medical reviewer recognizes that it is difficult to assess from clinical slides the margins of the actinic keratoses, so it is possible that the erythematous and edematous reaction actually was confined to the areas treated with LEVULAN®, but the reviewer thinks it more likely that the reaction can extend beyond the borders. In some patients (#18103, #18302), the area with erythema and edema appears two- to three- fold larger than the area with the actinic keratosis.

The following table depicts the degree of severity of burning/stinging during and/or 24 hours after photodynamic therapy. The majority of treated patients characterized as severe the degree of burning/stinging on at least one target lesion during treatment.

Severity of Burning/Stinging during and/or 24 hours after photodynamic therapy: ALA-018**

	FACE				SCALP			
	ACTIVE		VEHICLE		ACTIVE		VEHICLE	
Degree of Severity:	MILD/ MODER-ATE	SEVERE	MILD/ MODER-ATE	SEVERE	MILD/ MODER-ATE	SEVERE	MILD/ MODER-ATE	SEVERE
Burning/Stinging	30/72 (42%)	41/72 (57%)	10/21 (48%)	0/21	8/16 (50%)	8/16 (50%)	3/8 (38%)	0/8

**the fraction of patients who experienced burning/stinging on at least one target lesion up to (and not exceeding) the degree of severity indicated, during the time period between baseline and 24 hours after light treatment

From Data Listing 17, Vol. 1.56

The mean lesion number for patients who experienced severe discomfort was 6.48, while the mean lesion number for lesions in the active treatment arm was 6.98. Sponsor did not collect information that would permit the reviewer to determine if the severity of burning/stinging was related to the precise location within the scalp or face. Some patients at all the study centers reported severe discomfort. Patients with exclusively Grade 1 lesions, and patients with exclusively Grade 2 lesions, reported severe discomfort. Sponsor claims that discomfort [burning/stinging] starts declining in severity during or immediately after light treatment (from label's information to patients: "these feelings of discomfort [photodynamic response], if any, will improve at the end of light treatment"). There were 108 treatments (including first treatments and re-treatments) in which any burning/stinging was experienced. Following 64 of these occasions, burning/stinging was less severe at one minute after treatment compared to the most severe pain experienced during treatment. In comparison, on 44 occasions discomfort was as severe or more severe at one minute after treatment compared to the most severe discomfort experienced during treatment. In a significantly higher proportion of treatments ($p<.05$, one-sided z-approximation of the binomial distribution), the severity of discomfort was less at one minute after treatment compared to the most severe discomfort experienced during treatment. No or minimal discomfort was noted by patients by 24 hours after treatment.

Sponsor claims that "in the Phase III studies, stinging/burning and discomfort was less severe in those patients whose AK lesions were retreated with LEVULAN after eight weeks." In comparing burning/stinging between the first and second treatments in the same patients, the most striking observation is that there are fewer lesions undergoing retreatment than had undergone first treatment: the average number of lesions undergoing first treatment is 6.08, with standard deviation of 3.13, while the average number of lesions undergoing retreatment is 3.25, with standard deviation of 2.78. There were five patients who experienced retreatment who had the same number of target lesions at enrollment and at week 8. The sum of the burning/stinging scores during and immediately after treatment was calculated for these five patients: 3 had increased scores upon retreatment, 1 had a decreased score, and 1 had the same score. The major reason

why patients experienced less burning/stinging upon retreatment appears to be that patients had fewer lesions treated at Week 8.

Incidence and Severity of Cutaneous Adverse Events, post-PDT***: ALA-018

	FACE				SCALP			
	ACTIVE		VEHICLE		ACTIVE		VEHICLE	
Degree of Severity:	MILD/ MODER-ATE	SEVERE	MILD/ MODER-ATE	SEVERE	MILD/ MODER-ATE	SEVERE	MILD/ MODER-ATE	SEVERE
Scaling/Crusting	49/72 (68%)	1 (1%)	8 (38%)	0	9 (56%)	1 (6%)	3 (38%)	0
Pain/Tenderness	0	1 (1%)	0	0	1 (6%)	0	0	0
Itching	27/72 (38%)	2 (3%)	4 (19%)	0	5 (31%)	3 (19%)	2 (25%)	0
Ulceration	4/72 (6%)	0	0	0	0	0	0	0
Bleeding/ Hemorrhage	2/72 (3%)	0	0	0	1 (6%)	0	0	0
Hypo/ Hyperpigmentation✞	18/72 (25%)		4/21 (19%)		5/16 (31%)		2/8 (25%)	
Vesiculation	3/72 (4%)	0	0	0	1 (6%)	0	0	0
Pustules	3/72 (4%)	0	0	0	0	0	0	0
Oozing	1/72 (1%)	0	0	0	0	0	0	0
Dysesthesia	2/72 (3%)	0	0	0	0	0	0	0
Scabbing	3/72 (4%)	1 (1%)	0	0	0	0	0	0
Erosion	8/72 (11%)	1 (1%)	0	0	0	0	0	0
Wheal/Flare	2/72 (3%)							
Skin disorder, NOS	5/72 (7%)	1 (1%)	1 (5%)	1 (5%)	1 (6%)	0	1 (13%)	0

***defined as adverse events that are not present at baseline A. If a patient had an event recorded at more than one visit, that patient is counted only once.

✞This category refers to the fraction of patients who develop hypo- and/or hyper- pigmentation on at least one target lesion during the treatment course. Sponsor has not collected data that would permit the classification of the hypo- and/or hyper- pigmentation as mild, moderate, or severe.

om Data Listing 13, 19, Vol. 1.56

In the process of generating the above table, reviewer has clustered together related PDT responses [crusting, scaling, and hyperkeratosis grouped into scaling/crusting; hemorrhage and mild bleeding grouped into bleeding/hemorrhage; pain and tenderness grouped into pain] to eliminate clinically unimportant distinctions. Miscellaneous cutaneous adverse events [e.g., swollen cheek, warm sensation, herpes simplex, rash (2 events)], are classified as Skin disorder, NOS.

Both intensity and duration of an adverse event are relevant in assessing its impact on the patient. The duration of pain (experienced by patient 18106) was 22 minutes; the duration of tenderness (in patient 18303) was 6 days. Patients 18106, 18116, 18117, and 18501 developed ulcers that lasted 2 days, 3 days, 1 day, and 27 days, respectively.

In response to medical reviewer's request, sponsor submitted clinical slides of patients who developed ulcers following PDT. As judged from the submitted slides, all ulcers healed without leaving evidence of scar formation.

Laboratory Evaluations

For patients enrolled in the active treatment arm, mean hematocrit decreased from 44.04 at screening to 43.67 at Day 2. Compared to the percentage of patients in the active treatment arm with hematocrit levels below the normal range at screening (6%), more patients had abnormally low hematocrit levels at Day 2 (12%). This was higher than the percentage of patients in the vehicle arm with abnormally low hematocrit levels at Day 2 (7%). Five patients [18107, 18202, 18223, 18510, and 18703] had hematocrit levels within the normal range at screening that subsequently fell below the normal range by Day 2. The mean decrease in hematocrit levels for these five patients was 2. None of the changes in hematocrit were dramatic or of direct concern clinically: Patient 18704 had the lowest hematocrit level among active-treatment patients at Day 2 (value of 32), but this value was not substantially lower than what had been observed at baseline (32.3). Two of these five patients underwent retreatment, but only one again experienced a drop in hematocrit. The five patients had no common concomitant medications, no common medical condition, and did not have an unusually large number of treated lesions.

Reviewer's Comment: It would be appropriate to perform a Phase 4 safety study to confirm that any treatment-induced decrease in hematocrit is small and not clinically relevant.

Two patients in the LEVULAN®-treated arm (nos. 18103, 18106), but no vehicle-treated patients, had slightly elevated urinary levels of aminolevulinic acid on Day 2. These two patients each had six target lesions treated.

8.3.1.8 Reviewer's Comments/Conclusions of study results

This clinical study convincingly demonstrated that LEVULAN® is effective for treatment of multiple actinic keratoses of the face. Among patients with scalp lesions, a

higher percentage of patients in the active treatment completely cleared all lesions compared to the patients in the vehicle treatment, but the difference did not reach statistical significance. The likely reason for this failure to reach statistical significance is that comparatively few subjects with scalp lesions were enrolled in this trial. Within the limited time frame of this trial, the vast majority of lesions that achieved complete remission remained in remission. Re-treatment with LEVULAN®/blue light at week 8 of those lesions not in complete remission resulted in a significant increase in the complete clearance rate at week 12. Treatment is more effective for thinner lesions.

The preponderance of recorded adverse events were cutaneous, as would be expected for a topical treatment in which limited systemic absorption of the drug occurs. During and shortly after treatment, erythema and burning/stinging occurs for every patient, usually in most of the target lesions. Half the LEVULAN®/blue light treated patients experience edema at the target lesions. These adverse events largely resolved within a week after treatment. Other commonly experienced (>5%) cutaneous adverse events included scaling/crusting, itching, ulceration, hypo/hyperpigmentation, erosion, and miscellaneous cutaneous disorders. These events were predominantly mild to moderate in severity and short-lived. The only noteworthy treatment-emergent laboratory abnormality was a decrease in hematocrit, observed in a subset of the patients, that was not clinically significant.

8.3.2 Trial #2—ALA-019

8.3.2.1 Objective/Rationale/Design

Identical to ALA-018.

8.3.2.2 Protocol Overview

All aspects of this protocol, including procedures, evaluability criteria, defined endpoints, and statistical considerations, were identical to ALA-018. ALA-019 was conducted at 8 centers. 126 patients were randomized: 93 to receive LEVULAN® and blue light, and 33 to receive vehicle and blue light. Four patients in the LEVULAN® arm and 2 patients in the vehicle arm discontinued from the study.

Patient Discontinuations: ALA-019

Patient Number	Treatment Arm	Reason for Discontinuation	Time of Last Efficacy Measure
19102	LEVULAN®	Patient Non-Compliance	Week 8
19107	LEVULAN®	Patient Discontinued (out of town)	Week 12
19410	LEVULAN®	Patient Death (due to widespread carcinoma)	Week 4
19702	LEVULAN®	Patient Non-Compliance	Week 9
19108	Vehicle	Patient Discontinued	Week 9
19714	Vehicle	Patient Discontinued	Week 1

8.3.2.3 *Study Results*

8.3.2.3.1 Demographics, Evaluability

Summary of Baseline Demographic and Disease Characteristics: ALA-019

Characteristic	LEVULAN® (N=93)	Vehicle (N=33)	Overall (N=126)	p-value[a]
Age (years)				
N	93	33	126	0.318
Mean (SD)	67.1 (11.8)	64.7 (12.1)	66.5 (11.9)	
Range	38 – 89	35 – 85	35 - 89	
Sex				
Female	19 (20%)	2 (6%)	21 (17%)	0.059
Male	74 (80%)	31 (94%)	105 (83%)	
Skin Type[b]				
I	33 (35%)	11 (33%)	44 (35%)	0.565
II	44 (47%)	13 (39%)	57 (45%)	
III	15 (16%)	8 (24%)	23 (18%)	
IV	1 (1%)	1 (3%)	2 (2%)	
Race				
White	93 (100%)	33 (100%)	126 (100%)	
No. of Lesions / Patient				
4-7	43 (46%)	12 (36%)	55 (44%)	0.349
8-11	31 (33%)	10 (30%)	41 (33%)	
12-15	19 (20%)	11 (33%)	30 (24%)	
Location				
Face	67 (72%)	20 (61%)	87 (69%)	0.208
Scalp	26 (28%)	13 (39%)	39 (31%)	
Total Number of Lesions	788	303	1091	
Lesion Grade				
0[b]	0 (0%)	0 (0%)	0 (0%)	0.003
1	429 (54%)	192 (63%)	621 (57%)	
2	359 (46%)	111 (37%)	470 (43%)	
3[b]	0 (0%)	0 (0%)	0 (0%)	
Pigmentation Scale				
0	653 (83%)	274 (90%)	927 (85%)	0.002
1	125 (16%)	24 (8%)	149 (14%)	
2	10 (1%)	5 (2%)	15 (1%)	

Note: Percentages were calculated based on the number of patients with non-missing values in each treatment group.

[a] P-value is based on ANOVA with treatment for age and Cochran-Mantel-Haenszel general association test for sex and skin type.

[b] Skin Type:

I: White; always burns easily; shows no immediate pigment darkening reaction (IPD); never tans.
II: White; always burns easily; trace IPD; tans minimally and with difficulty.
III: White; burns minimally; IPD+; tans gradually and uniformly (light brown).
IV: Light brown; burns minimally; IPD++; always tans well (moderate brown).
V: Brown; rarely burns; IPD+++; tans profusely (dark brown).
VI: Dark brown or black; never burns; IPD+++; tans profusely (black).

Data Source: End-of Text-Tables 2, 3, and 4; Patient Data Listing 1, 3, and 4; and CRF pages 3, 5, and 7.

Source: Tables 11.2.1, 11.2.2, Vol 1.60. pp. 7-9587, 7-9589

Reviewer's Comment: There are no significant differences between the patients randomized to LEVULAN® or vehicle treatment. The demographic and baseline characteristics of the patients in ALA-019 and ALA-018 are quite similar in all respects. Some slight differences are that a higher percentage of patients in ALA-019 have skin type 1, they have more lesions per face and scalp, and a higher proportion of enrolled patients with scalp versus face lesions.

Evaluability by Center/Investigator: ALA-019								
	LEVULAN®				Vehicle			
	First Treatment			Second Treatment	First Treatment			Second Treatment
Investigator	Enrolled	ITT *	Evaluated at Week 8	Received/ Eligible#	Enrolled	ITT*	Evaluated at Week 8	Received/ Eligible#
D. CHEN Chicago, IL, U.S.A.	8	8	7	1/2♣	4	4	4	2/2
J. FOWLER Louisville, KY, U.S.A	12	12	12	1/1	4	4	4	4/4
L. HRUZA St. Louis, MO, U.S.A.	15	15	15	6/6	5	5	5	5/5
T. PHILIPS Boston, MA, U.S.A.	12	12	12	3/4	4	4	4	2/3
T. RALLIS Salt Lake City, UT, U.S.A	12	12	11	4/4	4	4	4	3/4
D. TASHJIAN Fresno, CA, U.S.A	10	10	10	10/10	4	4	4	4/4
C. TAYLOR Boston, MA, U.S.A	12	12	12	1/2	4	4	4	3/3
G. WEINSTEIN Irvine, CA, USA	12	12	12	5/5	4	4	3	3/3
*ITT: patients who are enrolled, randomized, and who receive LEVULAN® or vehicle								
♣Patient 19103, who missed visit 8, did not have 100% CR at weeks 4 or 12, and therefore was classified eligible								
Source: Vol. 1.60, Table 6.1 (pg. 7-9540) and Table 10.1.1, (pg. 7-9580) Data Listing 7								

Reviewer's Comment: The PDT Response presumably was not unbearably painful or unpleasant, as 91% (32/35) of the patients receiving LEVULAN®/blue light who were eligible for retreatment at week 8 were willing to undergo a second round of treatment.

Diana Chen, M.D. is identified as both the blinded and unblinded investigator for Center 1. This is a protocol violation. The other seven unblinded investigators were not physicians.

Reviewer's Comment: The quality of the safety data is rendered suspect because most of the unblinded investigators are not physicians. At the time of completion of this review, information about the qualifications of the unblinded investigator was not available. For Phase 4 studies to collect additional safety data, Agency should specify that both unblinded and blinded investigators are physicians.

8.3.2.3.2 Primary Efficacy Results

Response Rates at Week 8, ITT, L.O.C.F.: ALA-019

	Sponsor Analysis: 100% Complete Response Rate (Tables 22.5, 22.6, 22.7)				Agency Analysis: 100% Complete Response Rate			
	Active	Vehicle	95% Confidence Interval of difference	p-value	Active	Vehicle	95% Confidence Interval of difference	p-value
Total	59/93 (63%)	4/32 (13%)	36%-66%	<.001	59/93* (63%)	4/33♦ (12%)	36%-66%	<.001
Face	47/67 (70%)	4/19 (21%)	28%-71%	<.001	47/67 (70%)	4/20^ (21%)	28%-71%	<.001
Scalp	12/26 (46%)	0/13 (0%)	27%-65%	<.001	12/26 (46%)	0/13 (0%)	(27%-65%)	<.001
* This ratio differs slightly from that calculated by the statistical reviewer (58/93) because medical reviewer has not excluded from the count of cleared patients #19410, who achieved 100% CR at week 4, and was then lost to follow-up.								
♦ Denominator is 33 in the Agency ITT analysis. Patient 19714 is excluded from sponsor's LOCF analysis because of withdrawal from study because of patient non-compliance past week 1. Though there is no efficacy data on this patient, the patient should be included in ITT analysis. Changing the denominator from 32 to 33 will have a negligible effect on treatment outcome.								
^Denominator was changed from 19 to 20, for same reason as listed above.								

The noteworthy information to be extracted from this table includes:

(1) outcomes of patients treated with LEVULAN® and blue light were significantly superior to outcomes of patients treated with vehicle and blue light for all patients studied, for patients with facial lesions, and for patients with scalp lesions;

Patients with scalp or face lesions receiving active treatment had outcomes statistically superior to that of vehicle-treated patients, but patients with scalp lesions did not respond as well as did patients with facial lesions. One possible explanation for why patients with scalp lesions had poorer responses is that the mean lesion grade for scalp lesions (1.57) was significantly greater ($p<.01$) than the mean lesion grade for face lesions (1.39) , and lesions with higher grade did not respond as well to treatment (see below). treated with LEVULAN® and blue light were inferior to those of patients with facial lesions treated with LEVULAN® and blue light [this difference was not statistically significant [$p=.058$])

To reject the possibility that the results from one or a few of the centers drove the outcome depicted above, the 100% CR rate across the different study centers was examined (as depicted below).

100% CR Rate at Week 8 by Center/Investigator: ALA-019		
Investigator	LEVULAN®	Vehicle
D. CHEN Chicago, IL, U.S.A.	6/8 (75%)	2/4 (50%)
J. FOWLER Louisville, KY, U.S.A	11/12 (92%)	0/4
L. HRUZA St. Louis, MO, U.S.A.	9/15 (60%)	0/5
T. PHILIPS Boston, MA, U.S.A.	9/12 (75%)	1/4 (25%)
T. RALLIS Salt Lake City, UT, U.S.A	7/12 (58%)	0/4
D. TASHJIAN Fresno, CA, U.S.A	0/10 (0%)	0/4
C. TAYLOR Boston, MA, U.S.A	10/12 (83%)	1/4 (25%)
G. WEINSTEIN Irvine, CA, USA	7/12 (58%)	0/3

The only extreme outlying center (Dr. Tashjian's) has an unusually **low** 100% complete response rate for patients treated with LEVULAN®/blue light, so including the results from this center lowers the overall 100% CR. No single center exerts an untowardly positive effect on the primary efficacy variable. The consequence of removing the center in which the blinded and unblinded investigator was the same individual would have a minimal effect on the 100% CR rate (it would drop from 63% to 62%).

The following table shows that among LEVULAN® patients who had achieved 100% complete response by week 8, the majority remained clear of all their target lesions at week 12.

Remission Duration in Patients with 100% CR Observed at Week 8: ALA-019

Among patients with 100% CR rate observed at Week 8*	LEVULAN(%)(N=58✠)
100% CR MAINTAINED AT WEEK 12	48 (83%)
100% CR LOST AT WEEK 12	10 (17%)[6 of the patients (19101, 19413, 19506, 19511, 19705, 19713) had facial lesions recurring, 4 (19317, 19320, 19505, 19514) had scalp lesions recurring]
*The 100% CR rate observed at Week 8 was either achieved at Week 4 and maintained, or achieved at Week 8.	
✠The number of cleared patients counted in this table (58) is less than that counted in preceding table (59), because patient #19410 (who achieved 100% CR at week 4, and was then lost to follow-up) was excluded.	

Those subjects with any persistent target lesions at Week 8 were eligible for retreatment of those lesions at that time, following the same randomization scheme as in the original application. As depicted in the following table, evaluating the population of all patients, and the subset of patients with facial lesions, repeat treatment of persistent target lesions with LEVULAN®/blue light converted significantly more patients to 100% complete responses by week 12 than did repeat treatment with vehicle/blue light. For the subset of patients with persistent scalp lesions, retreatment with LEVULAN®/blue light trended toward a benefit, but the difference was not statistically significant (likely due to the small numbers of retreated patients).

Among Patients with Lesions Retreated at Week 8, Patients with 100% CR Rate at Week 12: ALA-019

	LEVULAN®	Vehicle	95% Confidence Interval of difference	p-value
Total	9/31 (29%)	2/26 (8%)	2%-40%	.026
Face	8/19 (42%)	2/14 (14%)	-1%-57%	.021
Scalp	1/12 (8%)	0/12 (0%)	-7%-24%	.527
Sources: Table 24.4, 24.5, and 24.6, Vol 1.60, pp. 7-9812 to 14				

The following table compares the lesion clearance rate for different lesion grades (outcomes for lesions of the same grade located on face and scalp are pooled for this analysis).

Lesion Complete Response Rate at Week 8, L.O.C.F. for different Lesion Grades: ALA-019

	LEVULAN®	Vehicle	95% Confidence Interval of Difference	p-value
Lesion Grade 1 (lesions are slightly palpable, and better felt than seen)	366/429 (85%)	81/187 (43%)	34%-50%	<.001
Lesion Grade 2 (lesions are moderately thick actinic keratoses, easily seen and felt)	282/359 (79%)	24/111 (22%)	48%-66%	<.001
Source: Tables 18.5, 18.6				

While the active treatment outcomes are significantly superior to those of vehicle treatment for each lesion grade, the complete response rate decreases as lesion grade increases.

8.3.2.3.3 Secondary Efficacy Results

As with study ALA-018, the protocol-specified secondary efficacy variables included investigator's and patient's cosmetic evaluation. Grading of cosmetic response of treated lesions and of overall response was in four categories: excellent, good, fair, and poor.

Cosmetic Evaluation of Lesion by Blinded Investigator, Week 12: ALA-018

Cosmetic Scale	LEVULAN®	Vehicle
Excellent	611 (80%)	70 (25%)
Good	79 (10%)	25 (9%)
Fair	43 (6%)	116 (41%)
Poor	27 (4%)	73 (26%)
Total	760	284
P value<.001 (Cochran-Mantel-Haenszel mean score test (RIDIT scores)		
Source: Table 11.4.1.6.1.		

Reviewer's Comment: The way these categories are defined permits investigator to capture in one grading scale (a) whether treatment has resolved a lesion, and (b) whether lesion resolution is accompanied by a cosmetically acceptable appearance. It is impossible to tease from the cosmetic evaluations the relative weights of these two effects in determining the "cosmetic" grade. That better "cosmetic" responses are observed following LEVULAN® treatment than vehicle treatment may reflect the higher likelihood of lesion cure following LEVULAN® treatment, and may not necessarily reflect aesthetically satisfactory outcomes with LEVULAN® treatment.

8.3.2.3.4 Safety

Extent of Exposure

93 subjects received one treatment of LEVULAN®/blue light and 31 subjects received two treatments of LEVULAN®/blue light

Discontinuations

No subjects were permanently or temporarily discontinued from the study due to laboratory abnormalities. No patients discontinued due to adverse events experienced during the light treatment.

Adverse Events

Local cutaneous adverse events (i.e., photodynamic response) were reported separately. Sponsor reports that 38 patients on active treatment and 12 patients receiving vehicle treatment experienced adverse events during this study. Sponsor's table below lists the number of patients with clinical adverse events, by body system and COSTART terminology. If a patient experienced more than 1 episode of an adverse event, the patient was counted only once for that event. If a patient had more than 1 adverse event in a body system category, the patient was counted only once in that body system total.

No. (%) of Patients with Clinical Adverse Events by Body System: ALA-019

Body System Category/ Adverse Event (COSTART)	LEVULAN® (N=93)	Vehicle (N=33)
With Any Adverse Events	38 (41%)	12 (36%)
Body as a Whole	21 (23%)	3 (9%)
Abdominal Pain	1 (1%)	0 (0%)
Accidental Injury	7 (8%)	1 (3%)
Chest Pain	1 (1%)	0 (0%)
Face Edema	1 (1%)	0 (0%)
Headache	6 (7%)	1 (3.0%)
Hernia	1 (1%)	0 (0%)
Infection	7 (8%)	1 (3%)
Neck Pain	1 (1%)	0 (0%)
Cardiovascular System	4 (4%)	0 (0%)
Bradycardia	1 (1%)	0 (0%)
Hypertension	3 (3%)	0 (0%)
Digestive System	4 (4%)	1 (3%)
Carcinoma of Liver	1 (1%)	0 (0%)
Colitis	1 (1%)	0 (0%)
Gastrointestinal Disorder	0 (0%)	1 (3%)
Jaundice	1 (1%)	0 (0%)
Melena	1 (1%)	0 (0%)
Nausea	1 (1%)	0 (0%)
Periodontal Abscess	0 (0%)	1 (3%)
Rectal Disorder	1 (1%)	0 (0%)
Tooth Disorder	1 (1%)	0 (0%)
Hemic and Lymphatic System	1 (1%)	1 (3%)
Blood Dyscrasia	0 (0%)	1 (3%)
Thrombocytopenia	1 (1%)	0 (0%)
Metabolic and Nutritional System	1 (1%)	0 (0%)
Creatinine Increased	1 (1%)	0 (0%)
Musculoskeletal System	5 (5%)	2 (6%)
Arthralgia	1 (1%)	1 (3%)
Arthritis	2 (2%)	1 (3%)
Myalgia	1 (1%)	1 (3%)
Tendon Disorder	1 (1%)	0 (0%)

(continued)

Table

No. (%) of Patients with Clinical Adverse Events by Body System

Body System Category/ Adverse Event (COSTART)	LEVULAN® (N=93)	Vehicle (N=33)
Nervous System	2 (2%)	2 (6%)
Anxiety	1 (1%)	0 (0%)
Insomnia	0 (0%)	1 (3%)
Neuritis	1 (1%)	0 (0%)
Vertigo	0 (0%)	1 (3%)
Respiratory System	4 (4%)	3 (9%)
Bronchitis	0 (0%)	1 (3%)
Cough Increased	1 (1%)	0 (0%)
Epistaxis	0 (0%)	1 (3%)
Laryngitis	1 (1%)	0 (0%)
Pharyngitis	1 (1%)	1 (3%)
Pneumonia	1 (1%)	0 (0%)
Sinusitis	1 (1%)	0 (0%)
Skin and Appendages	13 (14%)	2 (6%)
Acne	0 (0%)	1 (3%)
Dry Skin	1 (1%)	0 (0%)
Herpes Simplex	1 (1%)	0 (0%)
Maculopapular Rash	2 (2%)	0 (0%)
Rash	2 (2%)	0 (0%)
Skin Carcinoma	3 (3%)	1 (3%)
Skin Disorder	2 (2%)	0 (0%)
Skin Hypertrophy	2 (2%)	0 (0%)
Skin Ulcer	1 (1%)	0 (0%)
Special Senses	2 (2%)	1 (3%)
Conjunctivitis	1 (1%)	0 (0%)
Ear Disorder	0 (0%)	1 (3%)
Otitis Externa	1 (1%)	0 (0%)
Urogenital System	3 (3%)	2 (6%)
Hematuria	0 (0%)	1 (3%)
Polyuria	1 (1%)	0 (0%)
Prostatic Disorder	1 (1%)	0 (0%)
Urinary Tract Infection	1 (1%)	0 (0%)
Urine Abnormality	0 (0%)	1 (3%)
Data Source: End-of Text Table 31; Patient Data Listing 13; and CRF page 41.		

The six patients in the LEVULAN® arm who experienced serious adverse events (patients 19101, 19214, 19410, 19511, 19613, and 19802) experienced basal cell carcinoma (site unidentified), squamous cell carcinoma (right lower leg), liver failure and death (see section 10.1.1), pneumonia, automobile accident, and bradycardia.

Investigators considered these adverse events unrelated or remotely related to treatment, as does the medical reviewer.

Adverse Events: pre-PDT

42% of active treatment patients develop burning/stinging between Baseline A and B, while 6% of vehicle treatment patients develop burning/stinging; 10% of active treatment patients develop edema between Baseline A and B, while no vehicle treatment patients develop edema between Baseline A and B.

Reviewer's Comment: These results are either attributable to irritancy or to an inappropriate photodynamic response. Since no irritancy study has been performed with the to-be-marketed formulation, it is not possible to discern which of these two alternative explanations is correct.

Adverse Events: peri-PDT

The medical reviewer analyzed the prevalence of signs and/or symptoms expected during a photodynamic response observed during the period after LEVULAN® application until 24 hours after light treatment for patients undergoing active and control treatment, as is depicted below.

Prevalence of erythema, edema, and burning/stinging during and/or 24 hours after photodynamic therapy: ALA-019

	FACE				SCALP			
	ACTIVE		VEHICLE		ACTIVE		VEHICLE	
Fraction of patients with some or all target lesions involved:	SOME	ALL	SOME	ALL	SOME	ALL	SOME	ALL
Erythema♦	4/67	63/67	13/20	4/20	4/26	22/26	9/13	0
Edema♦	23/67	11/67	0	0	9/26	1/26	0	0
Burning/Stinging	7/67	60/67	3/20	0	1/26	25/26	3/13	1/13
*defined as the prevalence of adverse events during the time points at baseline B, through light treatment, and at 24 hours after light treatment ♦Sponsor has not collected data that would permit the classification of these adverse events as mild, moderate, or severe.								
From Data Listings 15, 16, and 18, Vol. 1.56								

Sponsor's analysis of the data listings (not shown) largely corroborated the medical officer's analysis. As was observed in clinical study ALA-018, the consequence of treatment with LEVULAN® and blue light was to increase the prevalence of patients who experienced erythema, edema, and stinging/burning associated with treated lesions in the period during and shortly after photodynamic therapy.

The photodynamic response experienced by active treatment patients was short-lived. As depicted in the following table, approximately half of the patients in whom all the target lesions were erythematous during and/or shortly after photodynamic therapy did not have all their target lesions erythematous at one week after treatment. The adverse events of edema and burning/stinging resolved more quickly, usually within 24 hours after completion of light therapy.

Patients with adverse events involving 100% of target lesions during photodynamic therapy: prevalence of erythema, edema, and burning/stinging at 24 hours and one week after therapy: ALA-019

	FACE				SCALP			
	ACTIVE		VEHICLE		ACTIVE		VEHICLE	
Fraction of patients with all target lesions involved:	24 hours	One week	24 hours	One week	24 hours	One week	24 hours	One week
Erythema	60/63	46/63	4/4	4/4	19/22	9/22	0	0
Edema	3/11	0	0	0	0	0	0	0
Burning/Stinging	9/60	1/60	0	0	2	2	0	0

From Data Listings 15, 16, and 18, Vol. 1.56

The following table depicts the degree of severity of burning/stinging during and/or 24 hours after photodynamic therapy. The majority of treated patients characterized as severe the degree of burning/stinging on at least one target lesion during treatment.

Severity of Burning/Stinging during and/or 24 hours after photodynamic therapy—ALA-019**

	FACE				SCALP			
	ACTIVE		VEHICLE		ACTIVE		VEHICLE	
Degree of Severity:	MILD/ MODER-ATE	SEVERE	MILD/ MODER-ATE	SEVERE	MILD/ MODER-ATE	SEVERE	MILD/ MODER-ATE	SEVERE
Burning/Stinging	26/67 (39%)	41/67 (62%)	1/20 (5%)	0	13/26 (50%)	13/26 (50%)	3/13 (23%)	0

**the fraction of patients who experienced burning/stinging on at least one target lesion up to (and not exceeding) the degree of severity indicated, during the time period between baseline and 24 hours after light treatment

From Data Listing 17, Vol. 1.63

Patients in the active arm underwent 124 treatments (including first treatments and re-treatments). Some degree of burning/stinging was reported at one or more of these time points for all these treatments. Following 85 of these occasions, burning/stinging was less severe at one minute after treatment compared to the average degree of

burning/stinging reported during treatment (at one, six and eleven minutes after light treatment was started). In comparison, on 39 occasions burning/stinging was as severe or more severe at one minute after treatment compared to the average discomfort experienced during treatment. In a significantly higher proportion of treatments ($p<.05$, one-sided z-approximation of the binomial distribution), the severity of discomfort was less at one minute after treatment compared to the average discomfort experienced during treatment. No or minimal discomfort was noted by patients by 24 hours after treatment.

Adverse Events: post-PDT

Prevalence and Severity of Cutaneous Adverse Events***: ALA-019

	FACE				SCALP			
	ACTIVE		VEHICLE		ACTIVE		VEHICLE	
Degree of Severity:	MILD/ MODER-ATE	SEVERE	MILD/ MODER-ATE	SEVERE	MILD/ MODER-ATE	SEVERE	MILD/ MODER-ATE	SEVERE
Scaling/Crusting	52/67	0	1/20	0	19/26	0	0	0
Pain	2/67	0	0	0	0	0	1/13	0
Itching	16/67	1/67	1/20	0	4/26	0	2/13	0
Ulceration	2/67	0	0	0	2/26	0	0	0
Bleeding/ Hemorrhage	3/67	0	0	0	0	0	0	0
po/ Hyperpigmentation✞	14/67		5/20		10/26		5/13	
Vesiculation	7/67	0	0	0	2/26	0	0	0
Pustules	3/67	0	0	0	0	0	0	0
Dysesthesia	1/67	0	0	0	0	0	0	0
Erosion	12/67	0	0	0	1/26	0	0	0
Wheal/Flare	9/67	1/67	0	0	1/26	0	0	0
Skin disorder, NOS	6/67	1/67	1/20	0	4/26	1/26	1/13	0

***defined as adverse events that are not present at baseline A. If a patient had an event recorded at more than one visit, that patient is counted only once.

✞This category refers to the fraction of patients who develop hypo- and/or hyper- pigmentation on at least one target lesion during the treatment course. Sponsor has not collected data that would permit the classification of the hypo- and/or hyper- pigmentation as mild, moderate, or severe.

From Data Listing 13, 19, Vol. 1.56

In the process of generating the above table, reviewer has clustered together related PDT responses [crusting, scaling, and hyperkeratosis grouped into scaling/crusting; hemorrhage and mild bleeding grouped into bleeding/hemorrhage; pain and tenderness grouped into pain] to eliminate clinically unimportant distinctions. Miscellaneous cutaneous adverse events (e.g., skin cancer, actinic keratosis, rash), which include together the adverse events by body system pertaining to the skin along with PDT responses, are classified as Skin disorder, NOS.

Though cutaneous adverse events are frequently observed, they are predominantly mild to moderate in severity and short-lived. The pain reported by two patients (19406, 19408) resolved within 3 to 4 hours. The ulcerations experienced by two patients (19302, 19303) resolved by 7 days and 3 days, respectively.

Laboratory Evaluations

The percentage of patients whose laboratory parameters fell outside the normal range was characterized for each of the 32 hematological and clinical chemistry laboratory parameters examined in this clinical study. For nine of these laboratory parameters [hematocrit, red blood cell count, neutrophil count, eosinophil count, AST, ALT, LDH, Alkaline Phosphatase, serum creatinine], a higher percentage of patients treated with LEVULAN® fell outside the normal range at Day 2 than did patients treated with vehicle who were measured at the same time point. For three of these parameters [hematocrit, red blood cell count, and eosinophil count], a higher percentage of patients treated with LEVULAN® fell outside the normal range at Day 2 than had fallen outside the normal range at baseline.

Mean hematocrit for patients in the active treatment arm decreased from 44.16 at screening to 43.91 at Day 2. Seven LEVULAN®-treated patients had low hematocrit level at Day 2, of whom six had low hematocrit values at screening. The patient with the lowest hematocrit level at Day 2 (patient 19303, at 32.2), had a screening hematocrit level of 33.5. (This patient had a past history of anemia). None of the changes in hematocrit levels were clinically significant.

The percentage of LEVULAN®-treated patients with urine levels of aminolevulinic acid above the normal range (up to 5.4 mg/dL) was lower at Day 2 than at screening. The mean urine level of aminolevulinic acid at screening was 2.17 mg/dL, with the mean increasing to 2.19 mg/dL at Day 2. These results suggest that if any topically applied aminolevulinic acid is absorbed, it is quantitatively metabolized (presumably to protoporphyrin IX).

8.3.2.4 Reviewer's Comments/Conclusions of study results

This clinical study convincingly demonstrated that LEVULAN® is effective for treatment of multiple actinic keratoses of the face and scalp. Within the limited time frame of this trial, the vast majority of lesions that achieved complete remission remained in remission at end-of-study. Re-treatment with LEVULAN®/blue light at week 8 of those lesions not in complete remission resulted in a significant increase in the complete clearance rate at week 12. Treatment is more effective for thinner lesions.

The preponderance of recorded adverse events were cutaneous, as would be expected for a topical treatment in which limited systemic absorption of the drug occurs. During and

shortly after treatment, erythema and burning/stinging occurs for every patient, usually in most of the target lesions. Half the LEVULAN®/blue light treated patients experience edema at the target lesions. Most of these adverse events resolved within a week after treatment. Other commonly experienced (>5%) cutaneous adverse events included scaling/crusting, itching, hypo/hyperpigmentation, wheal/flare, and miscellaneous cutaneous disorders. These events were predominantly mild to moderate in severity and short-lived. The only noteworthy treatment-emergent laboratory abnormality was a decrease in hematocrit, observed in a subset of the patients, that was not clinically significant.

9 Overview of Efficacy—Comparative results between and across studies

The outcome of the primary efficacy variable, 100% complete response rate, is strongly consistent across the two pivotal studies ALA-018 (68% CR rate) and ALA-019 (63% CR rate). The results are also consistent when the primary efficacy variable is examined as a function of the site of treatment (face vs. scalp). For face, the CR rate is 68% for ALA-018 and 70% for ALA-019; for scalp, the CR rate is 69% for ALA-018 and 46% for ALA-019. Ironically, the results for scalp in ALA-018 were not statistically significant but were statistically significant in ALA-019, even though the absolute value of the CR was higher in ALA-018. The reasons for this anomaly are two-fold: sample size was relatively small in the active treatment for scalp in ALA-018 (16 patients, versus 26 patients for ALA-019); and vehicle-treated patients in the scalp arm of ALA-018 had an anomalous 25% CR rate.

It is unclear why the CR rate in the scalp arm was substantially lower than the CR rate in the face arm. One possible explanation is that there were differences in the baseline characteristics of patients in the scalp and face arms. Scalp lesions on average were thicker than face lesions, and clearance rate appears to be lower for thicker lesions (possibly because less ALA penetrates the hyperkeratotic stratum corneum of thicker lesions). It is also possible that the flat light source is less effective at delivering a therapeutic amount of light to all lesions on a markedly curved surface such as the scalp, but more effective for a comparatively flat surface such as the face.

The following tables present pooled data from the pivotal studies showing the CR rates at week 8, percentage of patients undergoing re-treatment at week 8, efficacy of re-treatment at week 8, and response rates at week 12.

100% Complete Response Rate at Week 8, ITT, L.O.C.F.: pooled pivotal studies		
	LEVULAN®	Vehicle
Total	119/181 (65.7%)	8/62 (12.9%)
Face	96/139 (69.1%)	6/41 (14.3%)
Scalp	23/42 (54.8%)	2/21 (9.5%)

Percentage of Patients Undergoing Re-treatment at Week 8, I.T.T.: pooled pivotal studies		
	LEVULAN®	Vehicle
Total	56/181 (30.9%)	49/62 (79.0%)
Face	40/139 (28.8%)	31/41 (75.6%)
Scalp	16/42 (38.1%)	18/21 (85.7%)

Among Patients with Lesions Retreated at Week 8, Patients with 100% CR Rate at Week 12: pooled pivotal studies		
	LEVULAN®	Vehicle
Total	24/56 (42.9%)	2/49 (4.1%)
Face	21/40 (52.5%)	2/31 (6.5%)
Scalp	3/16 (18.8%)	0/18

100% Complete Response Rate at Week 12, ITT, L.O.C.F.: pooled pivotal studies		
	LEVULAN®	Vehicle
Total	129/181 (71.3%)	7/62 (11.3%)
Face	108/139 (77.7%)	5/41 (12%)
Scalp	21/42 (50%)	2/21 (9%)

Since the pivotal clinical studies were not designed to follow patients beyond 12 weeks after the initial treatment, there is no data on the long-term outcome (i.e., 6 or 12 months) of LEVULAN®-treated lesions.

10 Overview of Safety

Nine clinical studies performed by sponsor (Pharm-03, ALA-003A, ALA-007, ALA-008, ALA-012, ALA-016, ALA-017, ALA-018, ALA-019) involved exposure of patients to aminolevulinic acid solution.

Patients Exposed to Topical Aminolevulinic Acid

	Exposed Once	Exposed Twice
LEVULAN® (20% solution) and any Light)	339	87
LEVULAN® (20% solution) and blue light (any dosage)	296	83
LEVULAN® (20% solution) and 6-10.9 J/cm^2 Blue Light	232	66

Including all clinical studies, less than 300 patients have been exposed to LEVULAN® 20% solution and to 10 J/cm^2 Blue Light.

Reviewer's Comment: Complete and thorough safety assessment is not possible with such a small number of patients exposed to the to-be-marketed drug and light dose. Agency guidance calls for a minimum of 300 patients to be tested with the to-be-marketed formulation of new drugs. A Phase 4 study to assess more fully the local safety profile is warranted. Further, since all patients in ALA-018 and ALA-019 were Caucasians, there is no information available concerning the safety profile of LEVULAN® in other ethnic groups (e.g., Hispanics, Asians) who are at lower, but not zero, risk for development of actinic keratoses.

10.1 Significant/Potentially Significant Events

10.1.1 Deaths

ALA-017: One patient(#211), receiving 2.5% aminolevulinic acid solution treatment, died during study participation. He was a 71 year old male with a history of cardiovascular disease, who suffered a myocardial infarction and died in his sleep one month after application of solution and light treatment, with no adverse events. The investigator considered the event as not drug related. Medical reviewer agrees that this event is not drug related.

ALA-019: One patient(#19410), receiving active treatment, died during participation in study. During the treatment period, he underwent liver biopsy for diagnosis of jaundice and liver failure, was diagnosed with hepatocellular carcinoma, and subsequently expired at home. The patient had a long-standing history of alcoholism and cirrhosis. The investigator considered the jaundice to be mild in severity and remotely related to treatment and the hepatocellular carcinoma to be life-threatening and remotely related to treatment. The medical reviewer agrees that this death is attributable to the pre-existing liver disease and not to LEVULAN® treatment.

ALA-004: One patient (#211), receiving active treatment for superficial basal cell carcinoma with LEVULAN 20% in a cream formulation and broadband red light, died 11 days after study completion. The cause of death was congestive heart failure and aortic stenosis. He had a past medical history significant for congestive heart failure and atrial fibrillation. The investigator considered this death unrelated to drug treatment, and the medical reviewer agrees with this assessment.

10.1.2 Other Significant/Potentially Significant Events

In addition to the death described in section 10.1.1, ten patients in the active treatment arm of the pivotal studies experienced serious adverse events. Four of these adverse events [a pre-existing hyperkeratotic (Grade 3) actinic keratosis (at an untreated site), pre-existing squamous cell carcinoma on the left ear, basal cell carcinoma (site unidentified), squamous cell carcinoma (right lower leg)] would be expected to be found in a target population with multiple actinic keratoses. These adverse events are attributable to the patients' chronic UV exposure, not to a single exposure to LEVULAN®. The other serious adverse events in the pivotal studies [broken left leg (from accident), thalamic stimulator implant (to treat a tremor), ruptured abdominal hernia, pneumonia, automobile accident, and bradycardia seem unrelated to LEVULAN® exposure.

In drug dose ranging study ALA-017, six patients experienced serious adverse events: angina pectoris, bradycardia, basal cell and squamous cell carcinoma (in the same patient), syncope, and (benign) breast mass. These were pre-existing medical conditions or occurred more than one week after ALA and light treatment (except for the patient with angina pectoris, who experienced chest pain 6 days after light treatment). None of these serious adverse events appear to be drug related.

In light dose ranging study ALA-016, one patient experienced a serious adverse event (hospitalization due to chronic bronchitis, which occurred one month after treatment). This adverse event does not appear to be drug related.

10.1.3 Overdosage exposure

No overdosage information is available.

10.2 Other Safety Findings

10.2.1 ADR Incidence Tables

Adverse Events, pre-PDT

*Reviewer's Comment: Patient instructions in the protocols for ALA-018 and ALA-019 regarding how patients are to protect their treated lesions from light exposure during the time interval between LEVULAN® application and therapeutic light exposure ("*avoid direct exposure of target sites to sunlight or other high intensity light sources, including tanning light devices") *are ambiguous and could expose patients to phototoxicity. For example, a patient traveling by car on a sunny day would not have "direct exposure to sunlight" if the car windows were closed, but conceivably may be exposed to sufficient visible light through the windows to trigger an inadvertent phototoxic reaction. Also, the sponsor does not define the term "high intensity light source": is it a 70-watt*

reading bulb, an overhead fluorescent light, a TV screen, a fire in a fireplace? Though it is possible that a photodynamic response occurring at an inappropriate time (e.g. burning/stinging while reading under a reading lamp) might warn the patient that he or she is inadvertently being exposed inappropriately to intense light, it is also possible that the patient may instead ascribe the response to irritancy from the drug rather than phototoxicity from the drug/light combination, and not take remedial action. Further, burning/stinging is NOT universally experienced by patients during light treatment; it is conceivable that patients could experience an unpleasant long-term phototoxic reaction (e.g., ulceration and scarring) without experiencing burning/stinging during exposure to light.

Evidence form the adverse events reported from studies ALA-018 and ALA-019 suggest that inadvertent photodynamic responses from exposure to ambient light may be occurring: 44% of active treatment patients develop burning/stinging between Baseline A and B, while 10% of vehicle treatment patients develop burning/stinging; 13% of active treatment patients develop edema between Baseline A and B, while no vehicle treatment patients develop edema between Baseline A and B.

Adverse Events, peri-PDT

LEVULAN® treatment causes immediate, short-lived adverse events during PDT associated with the photodynamic response (e.g., erythema, edema, and burning/stinging) that usually resolve or return to baseline within 24 hours after light treatment, along with more long-lasting post-PDT cutaneous sequelae. The incidences of the peri-PDT adverse events and post-PDT adverse events for the pooled clinical studies are presented separately.

The following table depicts the incidence of signs and/or symptoms associated with a photodynamic response from the period including Baseline B until 24 hours after light treatment.

Incidence of erythema, edema, and burning/stinging during and/or 24 hours after photodynamic therapy: pooled pivotal studies

	FACE				SCALP			
	ACTIVE		VEHICLE		ACTIVE		VEHICLE	
Fraction of patients with some or all target lesions involved:	SOME	ALL	SOME	ALL	SOME	ALL	SOME	ALL
Erythema	12/139 (8%)	127/139 (91%)	25/41 (61%)	11/41 (27%)	6/42 (14%)	36/42 (86%)	13/21 (62%)	4/21 (19%)
Edema	46/139 (33%)	23/139 (17%)	0	0	14/42 (33%)	4/42 (10%)	0	0
Burning/Stinging	10/139 (7%)	128/139 (92%)	10/41 (24%)	2/41 (5%)	1/42 (2%)	41/42 (98%)	4/21 (19%)	3/21 (14%)
*defined as the prevalence of adverse events during the time points at baseline B, through light treatment, and at 24 hours after light treatment								
From Data Listings 15, 16, and 18, Vol. 1.56								

The global erythema and scales were designed to capture the frequency, but not the severity, of erythema and edema. Thus, sponsor has not collected data that would permit the classification of these adverse events as mild, moderate, or severe. Nonetheless, the adverse experiences that occur during the peri-PDT period presumably were not unbearably painful or unpleasant, as more than 90% of patients in the pooled pivotal studies receiving LEVULAN®/blue light who were eligible for retreatment at week 8 were willing to undergo a second round of treatment.

Severity of Burning/Stinging during and/or 24 hours after photodynamic therapy: pooled pivotal studies**

	FACE				SCALP			
	ACTIVE		VEHICLE		ACTIVE		VEHICLE	
Degree of Severity:	MILD/ MODER-ATE	SEVERE	MILD/ MODER-ATE	SEVERE	MILD/ MODER-ATE	SEVERE	MILD/ MODER-ATE	SEVERE
Burning/Stinging	56/139 (40%)	82/139 (59%)	11/41 (27%)	0	21/42 (50%)	21/42 (50%)	6/21 (29%)	0
**the fraction of patients who experienced burning/stinging on at least one target lesion up to (and not exceeding) the degree of severity indicated, during the time period between baseline and 24 hours after light treatment								
From Data Listing 17, Vol. 1.63								

Adverse events are undesired effects, whether or not there is attribution to a medicine or other cause. Analysis of adverse events should include the incidence and/or severity of signs/symptoms of phototoxic reactions and pigmentary changes.

The following table presents sponsor's analysis of the prevalence and severity of post-PDT cutaneous adverse events (medical reviewer's analysis substantially agrees with sponsor's analysis, except for the incidence of pigmentary changes). To avoid capturing in this incidence table those transient events immediately associated with the light treatment, adverse events are tabulated here if observed at visit B (Baseline B) only if present for more than 24 hours or if recorded at Visits 3 through 9 (the consequences associated with excluding transient adverse events are minimal). This table includes adverse events that arose during the second treatment.

...idence and Severity of Cutaneous Adverse Events Present Longer than 24 hours After Treatment: pivotal clinical studies

	FACE				SCALP			
	ACTIVE		VEHICLE		ACTIVE		VEHICLE	
Degree of Severity:	MILD/ MODER-ATE	SEVERE	MILD/ MODER-ATE	SEVERE	MILD/ MODER-ATE	SEVERE	MILD/ MODER-ATE	SEVERE
Scaling/Crusting	98/139 (70%)	1/139 (1%)	5/41 (12%)	0	27/42 (64%)	1/42 (2%)	4/21 (19%)	0
Pain	1/139 (1%)	0	0	0	0	0	0	0
Tenderness	1/139 (1%)	0	0	0	1/42 (2%)	0	0	0
Itching	35/139 (25%)	2/139 (1%)	3/41 (7%)	0	6/42 (14%)	3/42 (7%)	4/21 (19%)	0
Ulceration	6/139 (4%)	0	0	0	1/42 (2%)	0	0	0
Bleeding/ Hemorrhage	5/139 (4%)	0	0	0	1/42 (2%)	0	0	0
Hypo/ Hyperpigmentation✞ (M.O. analysis)	32/139 (23%)		9/41 (22%)		15/42 (36%)		7/21 (33%)	
Hypo/ Hyperpigmentation ...ponsor analysis)	48/139 (35%)		18/41 (44%)		26/42 (62%)		12/21 (57%)	
...irculation	5/139 (4%)	0	0	0	2/42 (5%)	0	0	0
Pustules	6/139 (4%)	0	0	0	0	0	0	0
Dysesthesia	3/139 (2%)	0	0	0	0	0	0	0
Oozing	1/139	0	0	0	0	0	0	0
Scabbing	3/139 (2%)	2/139 (1%)	0	0	0	0	0	0
Erosion	20/139 (14%)	1/139 (1%)	0	0	1/42 (2%)	0	0	0
Wheal/Flare	10/139 (7%)	1/139 (1%)	0	0	1/42 (2%)	0	0	0
Skin disorder, NOS	7/139 (5%)	0/139	1/20	0	5/42 (12%)	0/26	1/21 (5%)	0

*** If a patient had an event recorded at more than one visit, that patient is counted only once.

✞This category refers to the fraction of patients who develop hypo- and/or hyper- pigmentation on at least one target lesion during the treatment course. Sponsor has not collected data that would permit the classification of the hypo- and/or hyper- pigmentation as mild, moderate, or severe.

From Data Listing 13, 19, Vol. 1.56

There are no obvious differences in the frequency of any of the adverse events in listed in the above table, when patients in the scalp arm and face arm of the studies are compared.

M.O. and sponsor analysis agree that although a substantial fraction of patients acquire hypo- and/or hyperpigmentation during the study period, there does not seem to be a significant difference in the incidence of pigmentary changes between LEVULAN®-treated and vehicle-treated patients. There is no obvious explanation for why such a high percentage of patients in the vehicle-treated arm acquire pigmentary changes over the course of 12 weeks.

Reviewer's Comment: This result is surprising, as one would have predicted that certain patients would develop post-inflammatory hypo- or hyper-pigmentation as a consequence of the successful destruction of lesions. Any treatment-induced post-inflammatory pigmentary changes may have been obscured by the high background of pigmentary changes in the patients receiving vehicle.

10.2.2 Laboratory Findings, Vital Signs; ECGs

In both pivotal clinical studies, a subset of patients in the active treatment arm experienced a decrease in hematocrit levels associated with treatment. 7/183 (3.8%) of active treatment patients had hematocrit levels within the normal range at screening that fell below normal by Day 2 of treatment. In comparison, 1/62 (1.6%) of vehicle-treated patients had hematocrit levels within the normal range at screening that fell below normal by Day 2 of treatment. No patient experienced a decrease that was dramatic, and there is no indication that hematocrit decrease resulted in symptoms of anemia. No obvious mechanism suggests itself by which treatment with LEVULAN® and blue light could cause a drop in hematocrit.

Reviewer's Comment: Fitzpatrick et al. note that "about 11 percent of patients with EPP have a mild anemia of unknown cause (Fitzpatrick et al. Dermatology in General Medicine, Third edition, 1987)."

10.2.3 Special Studies

Retrospective Analysis of Patients with Inherited Porphyrias

The pathophysiology of two inherited metabolic diseases, erythropoietic protoporphyria (EPP) and acute intermittent porphyria (AIP), to some degree simulate the consequences of high-dose, systemic, chronic exposure of humans to protoporphyrin IX and aminolevulinic acid. Patients with EPP have a defect in the enzyme ferrochelatase, which converts PpIX to heme. These patients accumulate PpIX in many tissues, including skin, liver, erythrocytes, plasma, and feces. Patients with AIP have a defect in the enzyme porphobilinogen deaminase, which converts porphobilinogen to uroporphyrinogen III. These patients excrete excess ALA and porphobilinogen in their urine. Sponsor commissioned a study entitled "A Retrospective Study of Clinical History in Patients with Erythropoietic Protoporphyria (EPP) and Patients with Acute Intermittent Porphyria (AIP)" to evaluate the long-term consequences of chronic systemic elevation of PpIX, and of ALA and porphobilinogen, in patients with these inherited porphyrias. Three

investigators (Maureen Poh-Fitzpatrick, M.D., Micheline Matthews-Roh, M.D., and Karl Anderson, M.D.) performed a retrospective study extending back more than 20 years of 153 of their patients with EPP and 68 of their patients with AIP. The patients' clinical histories over time were examined as having possible relevance to the long-term toxicity of chronic overdosing with high-dose LEVULAN®. Sponsor is specifically interested in determining if chronic elevations in PpIX, ALA, or PBG are carcinogenic or teratogenic.

A retrospective analysis was performed of existing records (hospital records and physician files) of 153 patients with documented EPP and 68 patients with AIP. Supplemental information (e.g. causes of death of family members with inherited porphyrias) was obtained from telephone contacts. The average age at which EPP patients were diagnosed is 4 years. The median period of follow-up available exceeds 21 years, with 80% followed for greater than 11 years. The average age at which AIP patients are diagnosed is 28 years. The median period of follow-up is less than 5 years, with 15% of patients followed for greater than 11 years.

Causes of Death in Family Members of Patients with EPP and AIP		
	EPP	AIP
No. of Family Members Evaluated	629	302
No. of Reported Deaths	26	44
Cancer-Related Deaths	9*	4#
Deaths of Unknown Cause	3	10

*ovarian: 1, throat: 2, laryngeal: 1, lung: 2, liver: 1, breast: 1, bone: 1
#uterine: 1, liver: 2, bone: 1

Of the family members for whom a cause of death could be obtained, 39% of EPP family members succumbed to cancer, as did 11% of AIP family members. These numbers are consistent with sponsor's expectations for the relative frequency of cancer as the mortality cause. Interpretation of these results is difficult because no information on the age at death of these family members is available, making it impossible to assess the age-adjusted mortality rate.

All EPP and AIP patients were alive at the time of the retrospective analysis of their records. Among the patients with EPP, the most common clinical manifestation of illness was cutaneous phototoxicity, observed in up to 100% of the patients. Other clinical manifestations included a history of cholecystectomy or cholelithiasis, reported by 8% of patients, and ulcers, reported by 5% of patients. Two cases of ovarian cancer and two cases of cervical cancer (stages not specified) were diagnosed among the 67 female patients; sponsor claims that the reported incidence is consistent with the known lifetime risks of these cancers. The only reported dermatological complaint (ironically enough) was one case of actinic keratosis. None of the EPP patients reported significant ocular phototoxicity.

Among the patients with AIP, the common clinical manifestations included abdominal pain (experienced by all patients), nausea/vomiting (reported by 80% of patients), other GI disturbances, and psychiatric problems (reported by ~50% of patients). Eight instances of dermatological problems [cases of psoriasis (3), acne (2), eczema (1), urticaria (1), and genital herpes (1)] were recorded. One female patient (out of 61 in the study) was diagnosed with stage III ovarian cancer.

Pregnancy Outcomes in patients with EPP or AIP		
	EPP	AIP
No. of mothers with livebirths	25	34
No. of pregnancies	71	55
Congenital Defects	5*	0

*Congenital defects included: severe brain damage attributed to oxygen deprivation in utero from maternal septate uterus, ~~strawberry hemangioma~~, ~~umbilical~~ hernia (surgically repaired), hypospadias, and mitral valve prolapse.

Sponsor concludes that lifelong exposure to high systemic quantities of circulating ALA or PpIX do not predispose to cancer, and that they are not significantly genotoxic to the offspring of parents exposed to high circulating levels of ALA or PpIX.

Reviewer's Comment: While these study results are encouraging, the possibility that ALA, PBG, or PpIX are genotoxic or mutagenic cannot be definitively dismissed, because the number of patients whose records were examined in this ~~study is~~ relatively small. Similarly, the possibility that ALA, PBG, or PpIX are teratogenic cannot be dismissed on the basis of this retrospective study, because of the relatively small number of pregnancy outcomes recorded, and because no information is available to ~~assess~~ the frequency of stillbirths in this population.
The sponsor has performed several genotoxicity assays of aminolevulinic acid, which were negative (see Section 4, Animal Pharmacology and Toxicology and Dr. Nostrandt's Review). PpIX formation was not demonstrated in these assay systems, so the possibility that genotoxicity may result from unusually high levels of this metabolite induced by exogenous application of aminolevulinic acid cannot be excluded. Indeed, in one study cited by sponsor, positive genotoxic results were observed in cultured rat hepatocytes where PpIX formation was documented.

10.2.4 Drug-Demographic Interactions

In both pivotal clinical trials, all patients were white. Most enrolled patients had skin types 1, 2, or 3. It is impossible to draw conclusions about the safety or efficacy of LEVULAN®/ blue light administration for patients with skin types 4, 5, or 6 (i.e., for patients who are not white). To garner safety and efficacy data for this set of patients, sponsor should perform a Phase 4 study that enrolls some patients of African, Asian, and South American extraction. Though actinic keratosis is relatively rare in this set of

patients, it is not impossilbe to find some patients with this condition, especially among such patients with a comparatively light skin pigment.

10.2.5 Drug-Disease Interactions

The exclusion criteria for the pivotal clinical studies specified that the following sets of patients were ineligible for study enrollment: those with a history of cutaneous photosensitization, porphyria, hypersensitivity to porphyrins, photodermatosis, or inherited/ acquired coagulation defects. These patients were excluded because of concerns that they would be hypersensitive to side effects associated with LEVULAN® application/ blue light administration. Because these patients were excluded, it cannot be determined from the safety data of the two pivotal trials whether patients with these conditions would in fact be hypersensitive to the drug/light combination. Accordingly, the label for this product should indicate that patients with these conditions should not use it.

10.2.6 Drug-Drug Interactions

Patients were non-eligible for enrollment in the pivotal clinical trials if they were using photosensitizing drugs within a time frame where photosensitization from these drugs could still be present. This was one of the exclusion criteria because of the theoretical possibility that concomitant use of another known photosensitizing agent might increase the photosensitivity reaction of lesions treated with LEVULAN®.

There were no apparent treatment-emergent adverse reactions that resulted from drug-drug interactions.

10.2.7 Withdrawal Phenomena/Abuse Potential

No information about withdrawal phenomena or abuse potential is available.

10.2.8 Human Reproduction Data (if available)

No human reproduction data is available.

10.3 Safety Conclusions

Safety data from clinical studies suggest that LEVULAN®/ blue light causes short-lived local cutaneous adverse events in the majority of patients. Most patients experienced severe burning/stinging on at least one target lesion during or shortly after treatment, but this symptom resolves in virtually all patients by one week after treatment. The remainder of local cutaneous adverse events were mild or moderate in severity, and resolved spontaneously without need for treatment, usually within a week. There were no obvious treatment-emergent systemic adverse events. A small fraction of patients experienced a decrease in their hematocrit from within the normal range at screening to below the normal range after treatment, but the magnitude of these decreases were small and of no clinical significance. Less than 1% of patients had elevations in their urinary ALA levels marginally above the upper limit of normal, and this elevation was of no clinical significance.

While this safety profile is encouraging, complete and thorough safety assessment is not possible because only 232 patients have been exposed to the to-be-marketed drug and light dose during the drug development process. Agency guidance calls for a minimum of 300 patients to be tested with the to-be-marketed formulation of new drugs. A Phase 4 study to assess more fully the safety profile is warranted. Further, since all patients in ALA-018 and ALA-019 were Caucasians, there is no information available concerning the safety profile of LEVULAN® in other ethnic groups (e.g., Hispanics, Asians) who are at lower, but not zero, risk for development of actinic keratoses.

11 Labeling Recommendations

See Labeling Review

12 Recommendations

12.1 Approval, Approvable

It is recommended that this application be approved, provided that Phase 4 studies (as outlined below) are undertaken.

12.2 Phase 4 Studies

To permit more complete assessment of the safety profile of LEVULAN®/ Blue light, the following Phase 4 studies are suggested:

- Dermal irritancy study with LEVULAN®.
- Dermal allergenicity study with LEVULAN®
- Clinical efficacy and safety study in which LEVULAN® /Blue light are used in the manner as described in the proposed label. At least 70 patients should be enrolled. The blinded and unblinded investigators should be qualified health care professionals. To assess the safety profile in patients with skin types IV-VI, at least 30 patients with these skin types should be enrolled. To assess the long-term recurrence rate of actinic keratoses that have resolved after treatment with LEVULAN®/Blue light, patients should be seen in follow-up at one year after treatment.

12.3 Labeling changes

See labeling review

13 Signature block and distribution list

/S/ 7/1/99

Martin M. Okun, M.D., Ph.D.
Medical Reviewer

cc:
Archival NDA
HFD-540
HFD-540/Division Director/Wilkin
HFD-540/Dermatology Team Leader/Walker /S/ 7/2/99
HFD-540/Medical Reviewer/Okun

As above, Sponsor and AMO employed as the criterion for efficacy the proportion of subjects who achieved complete (100%) clearing of actinic keratoses. The Sponsor could address number of treatments needed and efficacy/safety in

19 **Page(s) Redacted**

Draft

Labeling